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# Initiation of reaction–diffusion waves of blood coagulation[☆]

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## HIGHLIGHTS

- Clot growth is described as traveling wave in the reaction–diffusion system.
- Critical initial condition for wave propagation is pulse solution.
- Existence of pulse solutions is proved using Leray–Schauder method.

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## ABSTRACT

Formation of blood clot in response to the vessel damage is triggered by the complex network of biochemical reactions of the coagulation cascade. The process of clot growth can be modeled as a traveling wave solution of the bistable reaction–diffusion system. The critical value of the initial condition which leads to convergence of the solution to the traveling wave corresponds to the pulse solution of the corresponding stationary problem. In the current study we prove the existence of the pulse solution for the stationary problem in the model of the main reactions of the blood coagulation cascade using the Leray–Schauder method.



## 1. Introduction

The main function of blood coagulation is the formation of blood clot covering the injury site and preventing further blood leak in case of vessel damage. One can define three main stages of the blood coagulation process: initiation of the clotting process, amplification of clot formation and clot growth arrest [1,2]. Clot growth is triggered by the enzyme thrombin that catalyzes fibrinogen conversion to fibrin which leads to blood gelation [3,4]. During each stage of the coagulation process the speed of thrombin formation is determined by the action of different proteins. Initial amount of thrombin is formed in response to the exposure of the tissue factor to blood plasma with help of factors VIIa and Xa [5,6], or as the result of factor XI activation on the foreign surface through the reactions of the contact system [7]. Amplification phase takes place thanks to the positive feedback loops of the blood coagulation cascade with participation of factors XI, X, IX, VIII, V and their complexes [8]. The main mechanisms of the clot growth arrest are the action of the direct thrombin inhibitors such as antithrombin [9], the mechanical removal of the active substances by the blood flow and the active protein C pathway [2]. Whether the amplification phase of the coagulation cascade will be launched or not depends on the amount of thrombin formed during the initiation stage [5]. In the current study we address triggering of the coagulation system from the initiation to the amplification phase using a mathematical model.

Clot growth can be described as a reaction–diffusion wave for the concentrations of blood factors [10–12]. Under certain assumptions we can prove existence and stability of such solutions for the model system of coagulation cascade [13]. We suppose that thrombin production during the coagulation process is described by a bistable system. Indeed, under normal conditions, accelerated thrombin formation occurs only in response to the significantly important initial stimuli [5,14,15]. Under this assumption, the convergence of the solution of the model system to a traveling wave takes place only for the sufficiently large initial condition. In terms of biochemical process, the amount of thrombin formed during the initiation stage must exceed some threshold value to launch the amplification phase of blood coagulation process. The threshold value for the initial conditions that guarantees convergence of the

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solution to the traveling wave in case of one PDE is a stationary solution of the system in particular form called pulse solution. The similar criteria was proven for the system of two equations in particular form [16]. In the current study we consider the existence of pulse solutions for a system of PDE describing the action of the coagulation cascade.

Thrombin production in quiescent plasma during the amplification phase of blood coagulation can be described by the following system of PDEs:

$$\begin{aligned}
\frac{\partial v_1}{\partial t} &= D\frac{\partial^2 v_1}{\partial x^2} + k_V T - h_V v_1,\\
\frac{\partial v_2}{\partial t} &= D\frac{\partial^2 v_2}{\partial x^2} + k_{VIII} T - h_{VIII} v_2,\\
\frac{\partial v_3}{\partial t} &= D\frac{\partial^2 v_3}{\partial x^2} + k_{XI} T - h_{XI} v_3,\\
\frac{\partial v_4}{\partial t} &= D\frac{\partial^2 v_4}{\partial x^2} + k_{IX} v_3 - h_{IX} v_4,\\
\frac{\partial v_5}{\partial t} &= D\frac{\partial^2 v_5}{\partial x^2} + k_X v_4 + k_X^* v_2 v_4 - h_X v_5,\\
\frac{\partial T}{\partial t} &= D\frac{\partial^2 T}{\partial x^2} + \left(k_{II} v_5 + k_{II}^* v_1 v_5\right)\left(1 - \frac{T}{T_0}\right) - h_{II} T.
\end{aligned} \tag{1.1}$$

Here $T$ denotes thrombin concentration, $v_i$, $i = 1, \dots, 5$, respectively denote concentrations of the activated forms of factors V, VIII, XI, IX and X. The constant $T_0$ denotes the maximal available concentration of thrombin taken equal to the initial concentration of prothrombin in blood plasma.

The diffusion coefficient $D$ is a positive number. We suppose that all the diffusion coefficients are equal to each other. Such assumption is relevant for the coagulation cascade reaction since all the participating proteins have approximately the same size. All results remain valid in the case of different diffusion coefficients.

We consider a one-dimensional case with $x$ axis perpendicular to the vessel wall and directed from the wall to the vascular lumen.

A more detailed discussion of the model can be found in [13], see also Appendix of this paper.

Let us set $\mathbf{w} = (w_1, \dots, w_5, T)$ (alternatively we will also denote $w_6 = T$). Then, system (1.1) can be written in the vector form:

$$\frac{\partial \mathbf{w}}{\partial t} = D\frac{\partial^2 \mathbf{w}}{\partial x^2} + \mathbf{F}(\mathbf{w}), \tag{1.2}$$

where $\mathbf{F} = (F_1, \dots, F_6)$, is the vector of reaction rates in Eqs. (1.1). The functions $F_i$ take the form:

$$\begin{aligned}
F_i(\mathbf{w}) &= \alpha_i(\beta_i T - w_i) \ \text{ for } \ i = 1, 2, 3,\\
F_4(\mathbf{w}) &= \alpha_4(\beta_4 w_3 - w_4),\\
F_5(\mathbf{w}) &= \alpha_5\left(\beta_5 w_4 + \gamma w_2 w_4 - w_5\right),\\
F_6(\mathbf{w}) &= \alpha_6 w_5(1 + \delta w_1)\left(1 - \frac{T}{T_0}\right) - \sigma T,
\end{aligned} \tag{1.3}$$

where the different constants are positive and are given by

$$\alpha_1 = h_V,\ \alpha_2 = h_{VIII},\ \alpha_3 = h_{XI},\ \alpha_4 = h_{IX},\ \alpha_5 = h_X,\ \alpha_6 = k_{II},$$
$$\beta_1 = \frac{k_V}{h_V},\ \beta_2 = \frac{k_{VIII}}{h_{VIII}},\ \beta_3 = \frac{k_{XI}}{h_{XI}},\ \beta_4 = \frac{k_{IX}}{h_{IX}},\ \beta_5 = \frac{k_X}{h_X},$$
$$\gamma = \frac{k_X^*}{h_X},\ \delta = \frac{k_{II}^*}{k_{II}},\ \sigma = h_{II}.$$

The zeros $\mathbf{w}^* = (w_1^*, \dots, w_5^*, T^*)$ of $\mathbf{F}$ satisfy the equations

$$\begin{aligned}
&w_1^* = \beta_1 T^*,\ w_2^* = \beta_2 T^*,\ w_3^* = \beta_3 T^*,\ w_4^* = \beta_3\beta_4 T^*,\\
&w_5^* = \beta_3\beta_4 T^*(\beta_5 + \gamma\beta_2 T^*).
\end{aligned} \tag{1.4}$$

Furthermore by expressing that $F_6(\mathbf{w}^*) = 0$ we find that $T^*$ is a root of some polynomial $P$ of order four which takes the form:

$$P(T) = TQ(T) \text{ with } Q(T) = aT^3 + bT^2 + cT + d. \tag{1.5}$$

Here $a < 0$ while the other coefficients of $P$ have no a priori signs (see Section 2.2 for the explicit values of the coefficients of $P$). Consequently the zeros of $F$ are in one-to-one correspondence with the ones of $P$. Clearly 0 is always a zero of $P$ and the corresponding zero of $F$ is the origin $\mathbf{0}$ of $\mathbb{R}^6$.

Hereafter we will focus on the case where $P$ has exactly two positive zeros denoted by $0 < \bar{T} < T^-$. We will also assume that

$$Q(0) < 0,\ Q'(\bar{T}) > 0,\ Q'(T^-) < 0, \tag{1.6}$$

(recall that $Q$ is some polynomial of order three with negative leading coefficient). It can be easily shown that $T^- < T_0$ (see Section 2.2).

Consequently, $\mathbf{F}$ has exactly three zeros in $\mathbb{R}_+^6$. Let us denote them by $\mathbf{w}^-$, $\bar{\mathbf{w}}$ and $\mathbf{w}^+$ where $\mathbf{w}^+ = \mathbf{0} < \bar{\mathbf{w}} < \mathbf{w}^-$ (here and everywhere below inequalities for vectors mean that each component of the vectors satisfies this inequality). Furthermore, assumptions (1.6) guarantee that the principal eigenvalue of the Jacobian matrix of $\mathbf{F}$ at $\mathbf{w}^\pm$ (resp. $\bar{\mathbf{w}}$) is negative (resp. positive) (see Section 3.3). Hence the nonlinearity $\mathbf{F}$ is of the bistable type.

It is easy to check that $F_i$ satisfy the following property for all $j \neq i$:

$$\frac{\partial F_i}{\partial w_j}(\mathbf{w}) \geq 0 \text{ if } w_k \geq 0 \text{ for } 1 \leq k \leq 5 \ \text{ and } \ T < T_0. \tag{1.7}$$

Hence the system is monotone in that region of $\mathbb{R}^6$ containing the positive zeros of $\mathbf{F}$. It has a number of properties similar to those for scalar equations including the maximum principle.

By virtue of the above properties, system (1.2) possesses a unique traveling wave solution $\mathbf{u}(z)$, $z = x - ct$, satisfying the following equations and limits at infinity:

$$D\mathbf{u}'' + c\mathbf{u}' + \mathbf{F}(\mathbf{u}) = \mathbf{0},\ \ \mathbf{u}(\pm\infty) = \mathbf{w}^\pm, \tag{1.8}$$

(up to some translation in space for $\mathbf{u}$).

The stationary solutions of system (1.2) satisfy the elliptic system:

$$\begin{aligned}
&Dw_i'' + \alpha_i(\beta_i T - w_i) = 0, \quad i = 1, 2, 3,\\
&Dw_4'' + \alpha_4(\beta_4 w_3 - w_4) = 0,\\
&Dw_5'' + \alpha_5\left(\beta_5 w_4 + \gamma w_2 w_4 - w_5\right) = 0,\\
&DT'' + \alpha_6 w_5(1 + \delta w_1)\left(1 - \frac{T}{T_0}\right) - \sigma T = 0.
\end{aligned} \tag{1.9}$$

Hereafter we consider system (1.9) on the real axis and look for an even positive solution vanishing at infinity:

$$\mathbf{w}(x) > \mathbf{0}, \quad \mathbf{w}(x) = \mathbf{w}(-x), \quad x \in \mathbb{R}, \quad \mathbf{w}(\pm\infty) = \mathbf{0}.$$

We will call such solutions pulses. Instead of the problem on the whole axis, we can consider system (1.9) on the half-axis $\mathbb{R}_+$ with the boundary condition

$$\mathbf{w}'(0) = \mathbf{0}. \tag{1.10}$$

We will look for the decreasing solutions defined on $\mathbb{R}_+$ and require:

$$\begin{aligned}
&\mathbf{w}'(0) = \mathbf{0}, \quad \mathbf{w}(x) > \mathbf{0} \ \text{ and } \ \mathbf{w}'(x) < \mathbf{0} \ \text{ for } \ x > 0,\\
&\mathbf{w}(\infty) = \mathbf{0}.
\end{aligned} \tag{1.11}$$

Then the pulse is obtained by extending this function on $\mathbb{R}$ by symmetry.

We can now formulate the principal result of this work.